REMARKS

Following entry of the amendment presented on June 24, 2005, claims 105-114, 116-119, 121-122, 124-127, 132-134, and 141-144 are pending in the application. Claims 106-109, 112, 113, 116-119, 121, 122, 124-127, 132-134, and 142-144 have been amended. The amendments to the claims are ministerial in nature.

In the final Office Action mailed March 24, 2005, claims 105-112 and 115-125, 127-132 and 134 were rejected under 35 U.S.C. §103(a) as obvious over US Pat. No. 5,395,825 - ("Feinberg"), in view of Lea *et al.*, Nocera *et al.*, Clark *et al.*, Thomas *et al.*, Thaler *et al.*, and Prakash *et* al. Claims 113 and 114 were rejected as obvious over Feinberg, in view of Lea *et* al., Nocera *et* al., Clark *et* al., Thomas *et* al., Thaler *et* al., and Prakash *et* al., Harlow *et* al., *and* Martin-Villa *et* al. Claim 126 was rejected as obvious over Feinberg, in view of Lea *et* al., Nocera *et* al., Clark *et* al., Thomas *et* al., Thaler *et* al., Prakash *et* al., and Grainger *et* al., and claim 133 was rejected as obvious over Feinberg, in view of Lea *et* al., Nocera *et* al., Clark *et* al., Thomas *et* al., Thaler *et* al., Prakash *et* al., and Heidenreich *et* al. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

Claims 105-114, 116-119, 121, 122, 124-127, 132-134 and 141-144 are pending for consideration, which is respectfully requested in view of the following remarks.

Scientific Background of the Invention:

The methods of the instantly claimed invention involve induction of immune tolerance in a prospective mother. By contrast, the secondary references cited by the Examiner deal with non-antigen specific immunosuppression (hereafter referred to as "generalised immunosuppression"). Generalised immunosuppression is very different from immune tolerance. Immune tolerance is antigen-specific whereas generalised immunosuppression is not antigen-specific. With the goal of furthering the understanding of the claimed invention, applicants provide below a brief discussion of generalised immunosuppression and immune tolerance and the distinctions between these different phenomena.

Generalised Immunosuppression v. Immune Tolerance

The immune system can be instructed not to destroy foreign antigen in a way that the inhibition is not antigen specific. In this case the immune system is systemically suppressed, leading to "generalized immunosuppression" – i.e. the suppression of immune responses directed against any and all antigens. Immunosuppressive drugs, such as cyclosporine, also induce generalized immunosuppression, where the immune system response is suppressed towards any and all antigens. For example, generalized immunosuppressive treatments for preventing graft rejection not only suppress transplanted graft rejection but also suppress other immune responses. One serious side effect of generalised immunosuppression is that it will place the host at risk of serious detrimental infection or tumour proliferation because the immune system, which normally controls these diseases by immune surveillance, is suppressed against any and all antigens.

In addition, however, the immune system can be instructed not to destroy a specific foreign antigen, while still destroying all other foreign antigens. This phenomenon, known as immune tolerance, is not a suppression of the immune response towards any and all antigens (i.e. "generalized" immunosuppression), but is a conducive active immune response towards a specific antigen. Immune tolerance is only brought about by inducing immunological tolerance with a specific antigen. A common example of induction of immune tolerance in clinical practice is the desensitization to specific environmental antigens in allergic individuals (e.g. hay fever or allergic rhinitis) by the controlled exposure to the particular antigen(s). Induction of immune tolerance requires a priming event, and involves a process of activation and expansion of immune mediating cells that proceeds over several days after the priming event. Huang et al, *J. Immunol.* 170:3945-3953 (2003). Generalised immunosuppression does not have an equivalent priming event, requires no preceding activation or expansion of mediating cells, and is a wholly unrelated immune phenomenon.

Moreover, the induction of generalised immunosuppression is immediate, resulting in changes in the proliferative ability of lymphocytes detectable within hours, and temporary, not even lasting days, because it is not memory related and can be reversed once the suppressive agent (e.g. cyclosporine) is removed from the environment. Bohler *et al.*, *Transplant Proc.* 30:2195- 7 (1998). Furthermore, the side effects experienced with generalised immunosuppression, where the immune system is suppressed against any and all antigens, do not occur during immune tolerance. Immune tolerance does not affect the ability of the immune system to mount immune

responses to other antigens. The immune system, when it is immune tolerant to a particular antigen or antigens (such as paternal antigens), is still fully functional and the host is not at risk of serious detrimental infection or tumour proliferation. Finally, generalised immune suppression is inconsistent with activation of immune tolerance since the priming, activation and expansion of the immune cells responsible for immune tolerance is inhibited by generalised immune suppression. Mihalyo *et al.*, *J Immunol.* 172:5338-45 (2004); Stock et al., *J Immunol.* 175:7380-7387 (2005). The induction of generalised immune suppression in a prospective mother would actually block induction of immune tolerance.

TGFβ has a very short half-life in vivo

The instant claims recite methods of inducing immune tolerance in a prospective mother by administering semen or paternal antigen and a TGFβ, prior to attempted conception. It is important to note that the *in vivo* half-life of TGFβ is on the order of only a few minutes (Wakefield *et al., J Clin Invest.* 86:1976-84 (1990); Philipa *et al., J Biol Chem.* 266:22290-6 (1991)). Accordingly, in the claimed methods, by the time a conceptus is present in the uterus, the TGFβ has long since been degraded and can have no direct biological effect on the conceptus.

Rejections under §103(a)

Claims 105-125 and 127-140 stand rejected under 35 U.S.C. §103(a) as obvious over US Pat. No. 5,395,825 ("Feinberg"), in view of Lea *et* al., Nocera *et* al., Clark *et* al., Thomas *et* al., Thaler *et* al., and Prakash *et* al. Claims 113 and 114 are rejected as obvious over Feinberg in view of Lea., Nocera, Clark, Thomas, Thaler, Prakash, Harlow *et* al., and Martin-Villa *et* al. The Examiner also has rejected claim 126 as obvious over Feinberg, in view of Lea, Nocera, Clark, Thomas, Thaler, Prakash, and Grainger *et* al. and claim 133 as obvious over Feinberg, in view of Lea, Nocera, Clark, Thomas, Thaler, Prakash , *and* Heidenreich *et* al. Applicants respectfully traverse.

All claims are presumed initially to be non-obvious. A *prima facie* case of obviousness requires three elements: (1) a teaching or suggestion of all of the claim limitations; (2) a suggestion or motivation to modify or combine the teachings of the applied prior art; and (3) a reasonable expectation of success in reaching the claimed invention. The Examiner bears the

initial burden of supporting any *prima facie* assertion of obviousness with adequate facts. MPEP § 2142 (Feb. 2000). Applicants respectfully submit that the Examiner has failed to provide adequate facts to support a *prima facie* case of obviousness here.

There would have been no motivation to combine the references

The Examiner asserts that Feinberg differs from the claimed invention "only in that the method of treating recurrent miscarriage by inducing immune tolerance by exposing mucosal surface of prospective mother with semen or MHC class I antigen of a prospective father capable of eliciting a Th-1 response and substantially purified TGFβ." August 1, 2005 Advisory Action at page 2.

The Examiner appears to assert that Feinberg teaches administering a combination of paternal antigen (semen) and TGFβ to a prospective mother, but concedes that Feinberg fails to teach or suggest any method of inducing immune tolerance in that prospective mother. Indeed, Feinberg fails to teach or suggest that the immune status of the mother is in any way relevant. Nevertheless, the Examiner asserts that this deficiency is remedied by the secondary references, which are cited as showing that TGFβ has, or at least may have, some generalised immunosuppressive effect on a mother. None of the secondary references teaches or suggest that TGFβ can play a role, in combination with paternal antigens, in inducing immune tolerance to the paternal antigens in a prospective mother.

Applicants respectfully traverse the rejection because there is no motivation to combine the cited references and, even if combined, the combination fails to teach or suggest the instantly claimed invention. Specifically, the combination of the cited references fails to teach or suggest methods of treating recurrent miscarriage by inducing immune tolerance to a paternal antigen in a prospective mother by exposing a mucosal surface of the prospective mother to (1) semen or an MHC Class I antigen of a prospective father and (2) a substantially purified TGFβ, where the exposure is at the time recited in the instant claims.

Rather, the Examiner's approach here is an improper hindsight reconstruction of applicants' claimed invention. In particular, the objectives of Feinberg and applicants' claimed invention are wholly different. Applicants' claimed invention recites methods of inducing tolerance to prevent adverse immunological reactions by the prospective mother that can result in

an immunologic rejection of the conceptus, and ultimately cause a miscarriage. By contrast, Feinberg is directed towards enhancing implantation of a conceptus (day 4) by inducing fibronectin production. The sole benefit of increased fibronectin productions is to aid in implantation. Fibronectin plays no role in alleviating adverse immunologic reactions, such as conceptus rejection. It is not surprising, therefore, that Feinberg makes no mention of the induction of tolerance or the impact TFGβ has on immunological mechanisms in prospective mothers.

Indeed, Feinberg's focus is limited to the competence of a conceptus towards uterine implantation (column 3 line 50) and methods of increasing the success rate of assisted reproduction (column 3 lines 66 to 67). Tellingly, Feinberg is completely silent regarding antigens of any kind, immunization of the prospective mother, or immune tolerance. Indeed, the Examiner admits that applicants' invention "is distinguishable from Feinberg because of Feinberg's failure to disclose or teach a method of treating infertility by inducing specific immune tolerance to a parental antigen in a mammalian prospective mother lacking said immune tolerance." Faced with the problem of miscarriages in a prospective mother, nothing within Feinberg would have suggested to a person of ordinary skill a method for inducing immune tolerance to a parental antigen in a mammalian prospective mother lacking immune tolerance.

The secondary references, cited for their purported disclosure of the potential immune effects of TGFβ, fail to cure the deficiencies of Feinberg. The secondary references, to the extent that they address the immune system at all, suggest that TGFβ may induce some type of generalized immune suppression, but fail to teach or suggest that;

(1) induction of immune tolerance is desirable

(2) nor do the secondary references suggest how tolerance might be induced

One of ordinary skill in the art therefore would not have been motivated to combine Feinberg with the secondary references to arrive at the instantly claimed invention. Applicants fail to understand how one of ordinary skill in the art would have been motivated to combine Feinberg, which makes no mention whatsoever of the role of the immune system in conception and miscarriage, with the secondary references which are completely silent to antigen-specific immune tolerance. The primary and secondary references are as different as apples and oranges,

and there would have been no motivation to combine them. Accordingly, no *prima facie* case of obviousness exists, and the rejection should be withdrawn.

None of the cited references, alone or in combination, teach or suggest administering a combination of TGFβ and paternal antigen at a time prior to conception to induce maternal tolerance

The methods recited in the instant claims are directed at altering the immune status of the mother. Specifically, miscarriage of an implanted conceptus can be prevented by inducing maternal tolerance to the implanted conceptus by administering both (1) paternal antigens and (2) TGFβ, at a time *prior* to conception. This timing of the administration of antigen and TGFβ as claimed is quite distinct from that taught or suggested by Feinberg. Nothing in Feinberg teaches or suggests that inducing tolerance in the mother would be in any way useful for preventing miscarriage and therefore there would have been no motivation for one skilled in the art to have modified the dosing regimen suggested by Feinberg to arrive at the methods recited in the instant claims.

By contrast, Feinberg describes a treatment regimen that is used to induce trophoblast fibronectin production rather than to induce immune tolerance in a prospective mother. For example, Feinberg "requires" TGFβ be delivered within a very short window for implantation - i.e., at day 4 ***after*** conception. This is logical since Feinberg's methods are aimed at increasing fibronectin production in the conceptus – it would be pointless to administer TGFβ until a conceptus is present and able to respond to the TGFβ. By contrast, claims 105 and 141 of applicants' invention, and the claims that depend therefrom, requires that TGFβ and paternal antigen delivery occurs at least a week or three months ***before*** attempted conception. This also is logical because the methods induce immune tolerance in the mother, *i.e.* lead to a reduction in the specific immune response against the paternal antigens on the conceptus. Feinberg neither suggests delivery of a combination of antigen and TGFβ, nor delivery of TGFβ prior to conception – there would be little point in delivering TGFβ at a time when the intended target of the TGFβ – the conceptus – is not present.

Feinberg states that "[t]he invention further provides methods of increasing the success rate of assisted reproduction comprising administering transforming growth factor β to ovum, sperm or conceptus prior to, simultaneously with, or following introduction of ovum, sperm or

conceptus into the reproductive tract of a female mammal." Paragraph bridging columns 3 and 4. Feinberg does not disclose or suggest, however, administering TGFβ a week or 3 months before attempted conception as recited in claims 105, 141, and their dependent claims. To that end, it is important to note that the ***in vivo*** half-life of TGFβ is only a few minutes, as described in Wakefield *et al*, and Philipa *et al, supra.*

In view of Feinberg's clearly stated objective of stimulating production of fibronectin by the conceptus, one skilled in the art would have understood that Feinberg could only have contemplated increasing the success rate of assisted reproduction if TGFβ is delivered precisely at the time during which the preimplantation embryo arrives in the uterine cavity, and not a week or months before attempted conception. Delivery of TGFβ at any other time would have no effect because the TGFβ would be degraded before it could contact the conceptus and have any effect on fibronectin production. Thus Feinberg fails to even remotely suggest that the TGFβ delivery occurs at least a week or three months before attempted conception.

The temporal limitations disclosed and claimed by applicants clearly distinguish and differentiate their invention from Feinberg. Feinberg therefore does not disclose or suggest all the elements of applicants' claimed invention and the rejection should be withdrawn.

None of the secondary references, either alone or in combination, cure the deficiencies of Feinberg

In light of Feinberg's complete failure to teach or suggest a TGFβ dosage regimen that is capable of inducing maternal tolerance, the Examiner seeks to rely on the teachings of Lea *et al.*, Nocera *et al.*, Clark *et al.*, Thomas *et al.*, Thaler *et al.* and Prakash *et al.* to provide the requisite disclosure or suggestion to use TGFβ under the conditions recited in applicant 'claims. However, none of these references, including Feinberg, taken either alone or in combination teach or suggest the use of TGFβ to treat recurrent miscarriage by inducing immune tolerance to a paternal antigen in a mammalian prospective mother lacking said immune tolerance. At best, Lea *et al.*, Nocera *et al.* and Clark *et al* suggest that TGFβ has generalized immunosuppression properties. However, generalised immunosuppression is not, and fails to even foreshadow, immune tolerance. There is no teaching or suggestion in any of the secondary references which would provide motivation for a person of ordinary skill in the art to combine Feinberg with any of the secondary references.

Applicants address the secondary references in turn:

Lea *et al.*

The Examiner asserts that Lea teaches that infertile patients with recurrent spontaneous abortion are deficient in TGFβ-producing suppressor cells in uterine tissue near the placental attachment site. However, as explained in more detail below, applicants respectfully submit that the Examiner reads far more into Lea than is there.

At page 61, second paragraph, Lea states that "...the immunosuppressive activity in supernatants conditioned by human decidua is mediated by a number of factors, among which is TGFβ2." Lea goes on to state at page 61, last paragraph, "What could be the role of TGFβ in human decidua and the significance of its absence?" Lea discussed several potential roles for TGFβ2, postulating for example that it could be immunosuppressive thus preventing damage against the conceptus by NK-LAK cells (see page 62) or that it TGFβ2 inhibits trophoblast invasion of the decidua (see page 62). In either event, Lea comes to no conclusion that would have motivated one of ordinary skill in the art to conclude that administration of exogenous TGFβ might be used in methods of inducing immune tolerance in a prospective mother.

Lea et al showed that TGFβ2-related molecules were released by decidual lymphoid cells and that *in vitro* that the supernatant from these cells was able to suppress the immune activity of normal human blood lymphocytes (Figure 1, page 56) and suppress the generation of cytotoxic T lymphocytes using the mixed lymphocyte culture-cytotoxic lymphocyte (MLC-CTL) assay (Figure 3, page 58). Lea et al's assay did not and could not show antigen-specific immune tolerance. At best, Lea only shows generalised immunosuppression *in vitro*. Generalised immunosuppression is not, and fails to even foreshadow, immune tolerance.

In sum, the Examiner's conclusion that Lea *et al.* teaches that TGFβ2 has immunosuppressive activity *in vitro*, which leads to induction of immune tolerance *in vivo* during the first trimester pregnancy in humans is incorrect. At the very most, Lea speculates that TGFβ may have a generalized immunosuppressive role during pregnancy. However, Lea would not have motivated a person skilled in the art at the time the present invention was made to administer to a prospective mother a factor capable of eliciting a generalized immunosuppressive response, to induce immune tolerance and treat recurrent miscarriage, since this would;

(1) have been expected to place the prospective mother at risk of a serious detrimental infection, for reasons discussed above; and

(2) have been expected to block the induction of immune tolerance, for reasons discussed above on page 10, first paragraph.

Nocera *et al.*

The Examiner alleges that Nocera teaches that human seminal plasma contains TGFβ, that is produced from high molecular weight latent TGFβ in the acid pH environment of the female lower genital tract, and that this seminal plasma TGFβ may immunologically protect the integrity of sperm. The Examiner further asserts that Nocera suggests that a reduced level of seminal plasma TGFβ may potentially render the spermatoza immunogenic and lead to attack by lymphocytes and other immune cells of the female host. Finally, the Examiner states that Nocera teaches that TGFβ has shown to inhibit the generation and killing activity of IL-2 activated NK cells (LAK).

The assay used by Nocera et al did not and could not show antigen-specific immune tolerance. The immune phenomenon describes by Nocera is, at most, generalized immunosuppression, and not immune tolerance. Indeed, Nocera *et al* would not have motivated a person skilled in the art at the time the present invention was made to administer to a prospective mother a factor capable of eliciting a generalized immunosuppressive response, to induce immune tolerance and treat recurrent miscarriage, since this would;

(1) have been expected to place the prospective mother at risk of a serious detrimental infection, for reasons discussed above; and

(2) have been expected to block the induction of immune tolerance, for reasons discussed above on page 10, first paragraph.

Clark *et al.*

The Examiner alleges that "Clark *et al.* teach that bioactive TGFβ is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive activity *in vivo* during the first trimester pregnancy in humans." The immunosuppression described by Clark is, however, generalized immunosuppression that is quite different from immune tolerance.

Clark *et al* showed that a TGFβ2-related molecule released from CD56+ cells obtained from decidua of human first trimester pregnancy was able to inhibit T lymphocyte generation in vitro (using the MLC-CTL assay).The assay used by Clark et al did not and could not show antigen-specific immune tolerance. Clark et al, at best, shows non-antigen specific generalised immunosuppression. The generalized immunosuppressive activity that Clark ascribes to TGFβ activity is quite different from immune tolerance, as described in detail above. Moreover, even if Clark were to suggest that generalized immunosuppression might somehow be useful in preventing recurrent miscarriage, no person skilled in the art at the time applicant's invention was made would administer a factor capable of eliciting an immunosuppressive response to a prospective mother, to induce immune tolerance and treat recurrent miscarriage, since it would;

(1) have been expected to place the prospective mother at risk of a serious detrimental infection, for reasons discussed above; and

(2) have been expected to block the induction of immune tolerance, for reasons discussed above on page 10, first paragraph.

Thomas *et al.*

The Examiner alleges that Thomas *et al.* teach that seminal plasma abrogates the postcoital T cell response to spermatozal histocompatibility antigens. Applicants respectfully do not see the relevance of this statement to the present invention. At most, Thomas suggests that seminal plasma has some undefined and unexplained immunosuppressive effect on the cellular immune reaction of the female to male antigens after mating (see abstract). Such a suggestion falls far short of any teaching or suggestion that induction of antigen-specific immune tolerance might be useful in treating recurrent miscarriage, let alone that tolerance might be induced using paternal antigens and TGFβ prior to conception in the manner recited in the instant claims. In any event, even if Thomas were to suggest that generalized immunosuppression might somehow be useful in preventing recurrent miscarriage, no person skilled in the art at the time of applicant would administer a factor capable of eliciting an immunosuppressive response to a prospective mother, to induce immune tolerance and treat recurrent miscarriage, as it would;

(1) have been expected to place the prospective mother at risk of a serious detrimental infection, for reasons discussed above; and

(2) have been expected to block the induction of immune tolerance, for reasons discussed above on page 10, first paragraph.

Thaler *et al.*

The Examiner alleges that Thaler teaches that seminal plasma regulates maternal immunity for insemination and pregnancy and that seminal plasma contains factors that specifically suppress the effects on female alloimmune response to paternally derived alloantigens. The Examiner further alleges that Thaler teaches that seminal plasma could prime mothers prior to fertilization for pregnancy acceptance and that improved implantation rates are observed in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamete intrafallopian transfer treatment cycle. (see abstract, in particular). Nothing in Thaler, however, describes that these alleged effects of seminal plasma are due to the presence of TGFβ in the plasma.

Moreover, if one of ordinary skill in the art were to read Thaler and draw the same inferences as the Examiner, they would surely have concluded that semen *alone* was sufficient to "prime" the prospective mother. There would have been no reason to administer TGFβ *plus* semen a week prior to attempted conception to induce maternal tolerance.

In any event, Thaler fails to suggest that a combination of TGFβ and paternal antigen might be useful for inducing maternal immune *tolerance* to paternal antigen prior to fertilization. There would have been no motivation to combine Feinberg, which merely suggests using TGFβ to induce fibronectin synthesis in the trophoblast, with Thaler, which does not refer at all to TGFβ, but merely suggests that seminal plasma has generalised immunosuppressive effects on female alloimmune response. Nothing in either reference, or indeed in any of the other secondary references, teaches or suggests the methods of the present invention, which involve inducing immune tolerance using a combination of paternal antigen and TGFβ prior to conception. Accordingly, withdrawal of the rejection respectfully is requested.

Prakash *et al.*

The Examiner alleges that Prakash *et al.* teach that exposing genital mucosal surface of a prospective mother to semen through coitus in the form of ejaculate is a form of immunization,

but that a potent inhibitor of the immune response was found in semen. As such, Prakash is cited for essentially the same proposition as Thaler and Thomas, namely that semen inhibits the immune response in a prospective mother. As such, Prakash fails as a reference for the same reasons described above for Thaler and Thomas, and the rejection should be withdrawn.

Even if the references could be combined, they fail to teach all of the claim limitations

Even if the references could, somehow, properly be combined, the combination would not have taught all the claim limitations. Specifically, nothing in the combination of references teaches or suggests administration of a combination of TGFβ and paternal antigen at a time *prior* to conception sufficient to induce maternal tolerance. None of the references teaches administration of this combination, for example, a week prior to attempted conception, as recited in claim 105. Accordingly, no *prima facie* case of obviousness exists and the rejection should be withdrawn.

Summary

In sum, the references cited by the Examiner, either alone or in combination, fail to teach or suggest induction of immune tolerance in a prospective mother by administering a combination of TGFβ and paternal antigen prior to conception. The rejection here seeks to use impermissible hindsight to pick and choose portions of the claimed invention from among a variety of references, when no motivation to combine the cited references can be found within the references themselves. Moreover, even if the references properly could be combined, that combination still would not teach or suggest the instantly claimed methods of inducing immune tolerance using a combination of paternal antigen and TGFβ prior to conception. Nowhere do the references nor their combination suggest either the desirability of inducing *antigen-specific* immune tolerance nor suggest that the administration of TGFβ and paternal antigen one week or 3 months before attempted conception can induce that tolerance. Accordingly, the rejection is improper and should be withdrawn.

The declarations of Drs. Carolyn B. Coulam and John C. Herr provide further explanation as to why the cited references fail to teach or suggest the desirability of inducing *antigen-specific* immune tolerance nor suggest that the administration of TGFβ and paternal antigen one week or 3

months before attempted conception can induce that tolerance. *See Declaration of Dr. Carolyn B. Coulam and Declaration of Dr. John C. Herr,* appended hereto as APPENDIX A and APPENDIX B, respectively.

The claimed invention has received recognition in the field

The declarations of Drs. Coulam and Herr also note that one of the coinventors of the instant application, Dr. Sarah Robertson, has received a prestigious award from the American Society for Reproductive Immunology. Drs. Herr and Coulam also state that Dr. Robertson's work on the role of immune tolerance in preventing miscarriage was a significant factor in her being awarded this honor. Appreciation by contemporaries skilled in the field of the invention is a useful indicator of whether an invention would have been obvious to such persons at the time it was made. *Vulcan Engineering v. Fata Aluminium,* 278 F.3d 1366, 1373 (Fed. Cir. 2002) The declarations by Dr. Coulam and Herr provide evidence that Dr. Robertson's colleagues recognized the groundbreaking nature of Dr. Robertson's work that forms the basis for the instantly claimed invention and is further evidence of the nonobviousness of the invention.

In addition, the work that formed the basis for the claimed invention has been recognized in prestigious journals. For example, the feature articles in the journals *Nature* and *New Scientist* appended hereto as APPENDIX C and APPENDIX D respectively, demonstrate that the work was regarded as a scientific breakthrough. These articles are further evidence of appreciation by contemporaries skilled in the field of the invention and further demonstrate the nonobviousness of the claimed invention. Accordingly, withdrawal of the rejection is requested.

CONCLUSION

Applicants respectfully assert that the amendments presented above should be entered as they place this case in condition for allowance by clarifying the invention and responding the Examiner's suggestions or concerns. In view of the amendment and remarks, applicants respectfully request that all objections and rejections be withdrawn and that a notice of allowance be forthcoming. The Examiner is invited to contact the undersigned attorney for applicants at (202) 912-2197 for any reason related to the advancement of this case.

Respectfully submitted,

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